

Illness, Severity, and Outcomes among Enteric Fever Cases: Data from the Surveillance for Enteric Fever in Asia Project (SEAP)

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Background

- Enteric fever can lead to severe illness, including prolonged hospital stays and clinical complications
 - Hallmark complication of typhoid is ileal perforation
 - Other reported complications: gastrointestinal bleeding, hepatitis, encephalopathy
- Few studies detail the severity of enteric fever and its outcomes
- Knowledge gaps surrounding the clinical spectrum of disease and long-term sequelae



Methods

- **Multi-country, multi-site, prospective, population-based surveillance**
- **3 years: September 2016 to August 2019**
- **Objective: Characterize the burden of enteric fever in selected settings in south Asia, including**
 - **Population-based incidence**
 - **Antimicrobial resistance**
 - **Cost of illness**
 - **Clinical spectrum of disease, including severity, complications and outcomes**



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Study Sites

Bangladesh

2 Pediatric hospitals

- Dhaka Shishu Hospital
- Shishu Sasthya Foundation Hospital

3 Lab network sites



Nepal

2 Hospitals

- Kathmandu Medical College and Teaching Hospital
- Dhulikhel Hospital

5 Lab network sites



Pakistan

2 Hospitals

- Aga Khan University Hospital
- Kharadar General Hospital

3 Lab network sites Surgical units from 2 additional hospitals



Case Definitions

- **Confirmed case:** Blood culture positive for *Salmonella* Typhi or Paratyphi
- **Surgical case:** Non-traumatic ileal perforation with no other known etiology, even in absence of microbial confirmation
- **Recurrent case:** Self-reported diagnosis of typhoid at follow up
- **Complication:** Diagnosis of a condition listed below, as documented by attending physician
 - Intestinal perforation
 - Gastrointestinal bleeding
 - Encephalopathy
 - Myocarditis
 - Endocarditis
 - Hepatitis
 - Sepsis
 - Pneumonia/pulmonary complications
 - Arthritis
 - Meningitis
 - Peritonitis
 - Endocarditis
 - Appendicitis

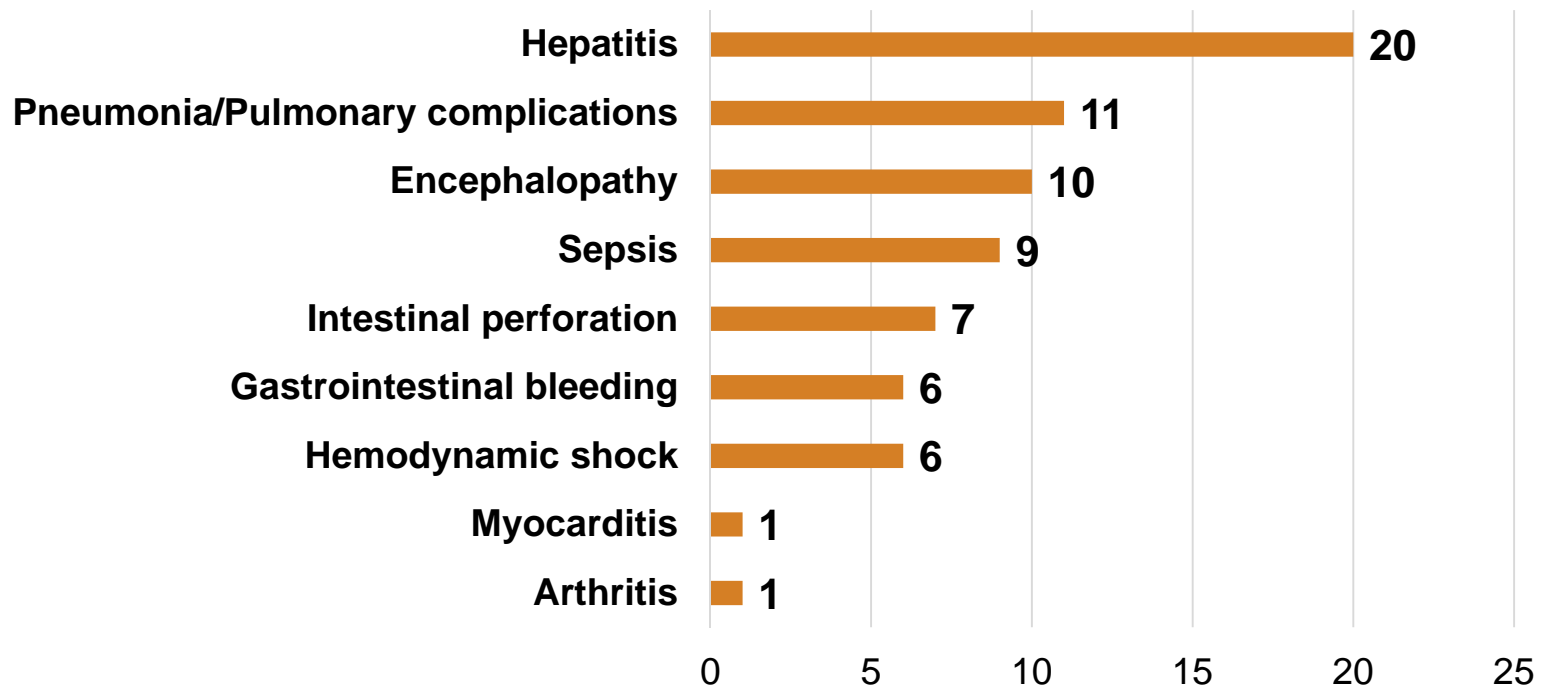
Results

Enrollment by Recruitment Location (Sep 2016 – Dec 2018)

	Enrolled n=23614	Blood culture positive n=6136
Hospital		
Outpatient/Inpatient	20097	2784
Hospital Lab	937	937
Surgical	170	5
<u>Total hospital</u>	21204	3726
Medical records reviewed	21174	3720
Laboratory networks	2410	2410

Complications[^] Developed Among Enteric Fever Cases (n=3720)

	Bangladesh n=2247	Nepal n=408	Pakistan n=1065	Total n=3720
Complications, any, n (%)	15 (0.7)	12 (2.9)	33 (3.1)	60 (1.6)
Complications, more than one, n (%)	1 (7)	1 (8)	6 (18)	8 (13)



[^]Ascertained via medical records at enrollment visit

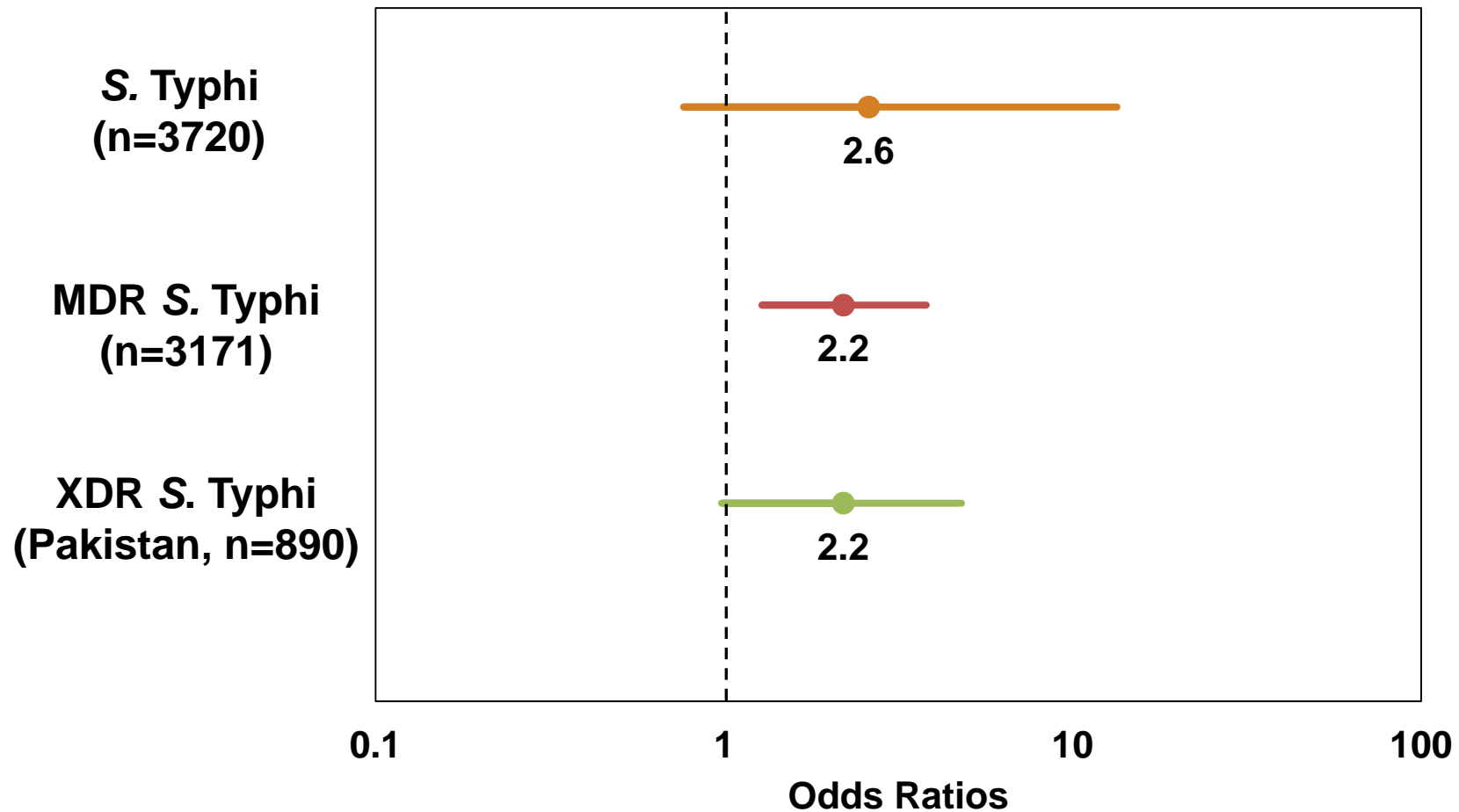
Characteristics of Complications[^] Among Enteric Fever Cases (n=3720)

	Developed Complications n=60	Did Not Develop Complications n=3660	p-value
Male sex	55%	56%	0.8324
Age in years, median (IQR)	9 (4-17)	6 (3-10)	0.0042
<u>Reported symptoms</u>			
GI symptoms	82%	48%	<0.0001
Respiratory symptoms	45%	30%	0.0148
CNS symptoms	22%	4%	<0.0001
Reported prior antibiotic use	70%	54%	0.0027
Measured temperature at presentation, median	102.2	100.9	0.0457

[^]Ascertained via medical records at enrollment visit

Respiratory symptoms: Cough, difficulty breathing;
GI symptoms: Vomiting, diarrhea, constipation, nausea;
CNS symptoms: Seizure, dizziness, confusion

Odds Ratios of Developing Complications by Organism and Antimicrobial Resistance Pattern

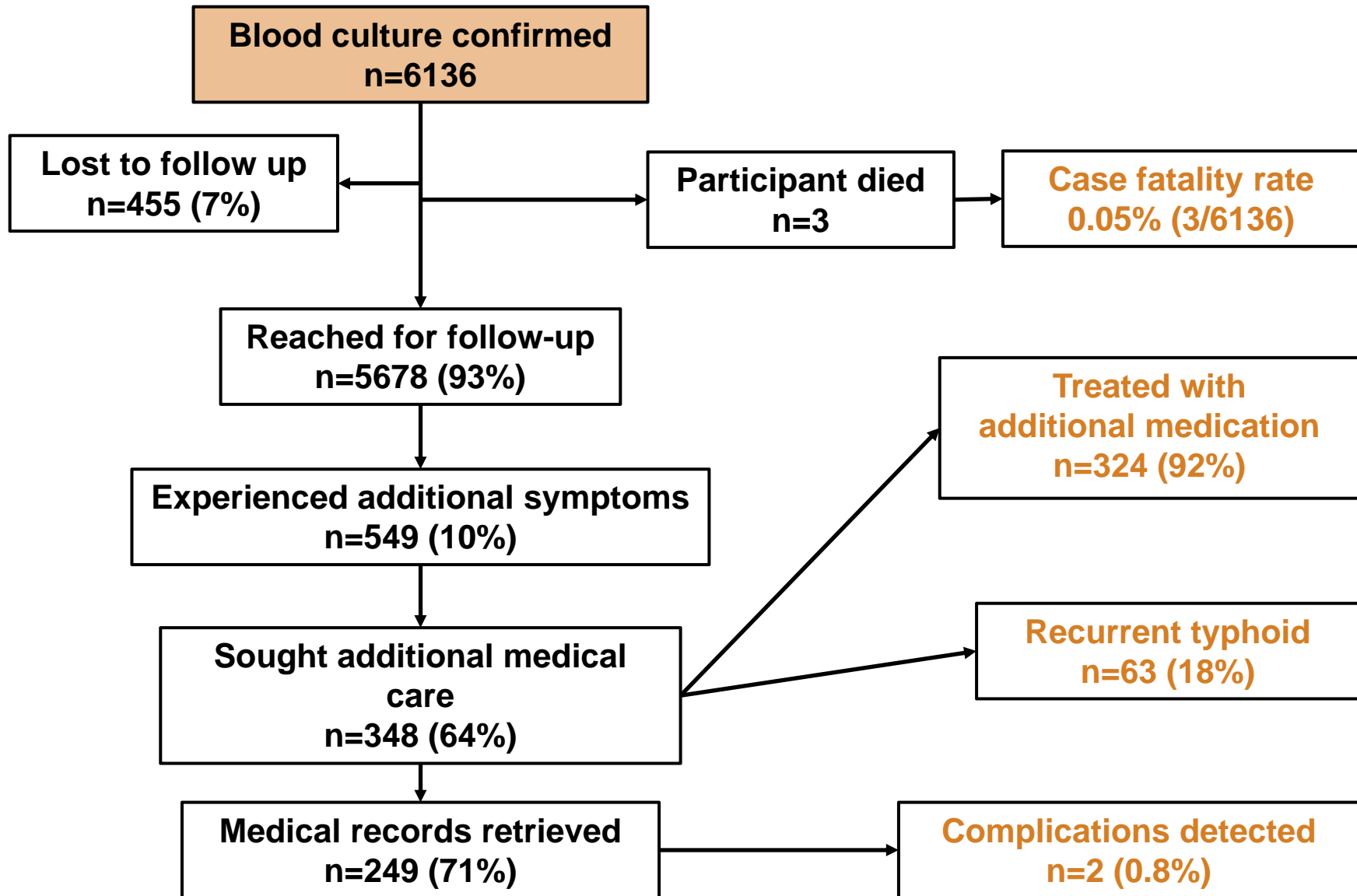


Multi-drug resistant (MDR): Resistant to ampicillin/amoxicillin, chloramphenicol, trimethoprim-sulfamethoxazole
Extensively drug resistant (XDR): MDR + resistant to ciprofloxacin, ceftriaxone

Other Markers of Severity of Typhoid

- **Days unable to do usual activities**
 - Median (IQR): 6 days (2-10)
- **Hospitalization**
 - 1939/6136 (32%) of cases were hospitalized
 - Children <2 years have highest proportion hospitalized (203/529, 38%)
- **Length of stay at hospitals**
 - Median (IQR): 5 days (3-7)
- **Bed occupancy at hospitals**
 - DSH: mean of 16 beds per night occupied by typhoid patients
 - April 2018: mean of 30 beds occupied per night

6-Week Follow Up



Characteristics of Suspected Enteric Fever-Related Ileal Perforations[^]

	n=177 (%)
<u>Country</u>	
Pakistan	171 (96)
Nepal	3 (2)
Bangladesh	3 (2)
<u>Pathogen detection methods</u>	
Pathology performed	30 (17)
Positive for <i>S. Typhi</i>	1 (3)
Blood culture performed	116 (66)
Positive for <i>S. Typhi</i>	7 (14)
XDR	4/5 (80)
Positive for <i>S. Paratyphi</i>	1 (2)
Male sex	127 (72)
Median age, IQR	13 (7-24)
Median days from onset of symptoms to presentation, (IQR) (n=111)	12 (7-20)
Prior antibiotic use	92 (52)
Median length of stay, (IQR) (n=118)	9 (6-14)
Died	15 (8)

[^]Non-traumatic with no other known etiology

Summary

- **Low rate of complications, but high proportion hospitalized and prolonged hospital stay**
- **Additional burden after enrollment visit**
- **Drug resistance was associated with more severe typhoid**
 - **Odds of developing a complication were higher among MDR and XDR cases**
 - **Majority of Typhi isolated from ileal perforations was XDR**
- **High proportion of previous antibiotic use among severe cases**

Limitations

- **Differences in clinical opinion**
 - **Discerning comorbidities from complications**
- **Ability to contact cases with severe outcomes**
 - **Asked for multiple phone numbers, including family members' numbers**
- **Reliance on care-seeking and blood culture**
 - **May miss severe cases that do not seek care**
 - **May miss severe cases not confirmed by blood culture**

Conclusions

- **Typhoid places a high burden on individual and health system**
 - **Could be alleviated with interventions to reduce disease, especially those under 2 years**
- **Antimicrobial resistance may be an important risk factor for complications**
 - **Individuals infected with MDR or XDR strains had a higher risk of complications**
 - **Empirical treatment in settings with high levels of antimicrobial resistance may risk complications due to ineffective therapy**
- **Lack of rapid and sensitive diagnostic may be a limitation to effective treatment at the first point of care**
 - **Could result in additional need for care**
- **Future analysis will look to understand which factors contribute to the development of severe disease**

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SEAP Presentations & Posters

Oral Presentations

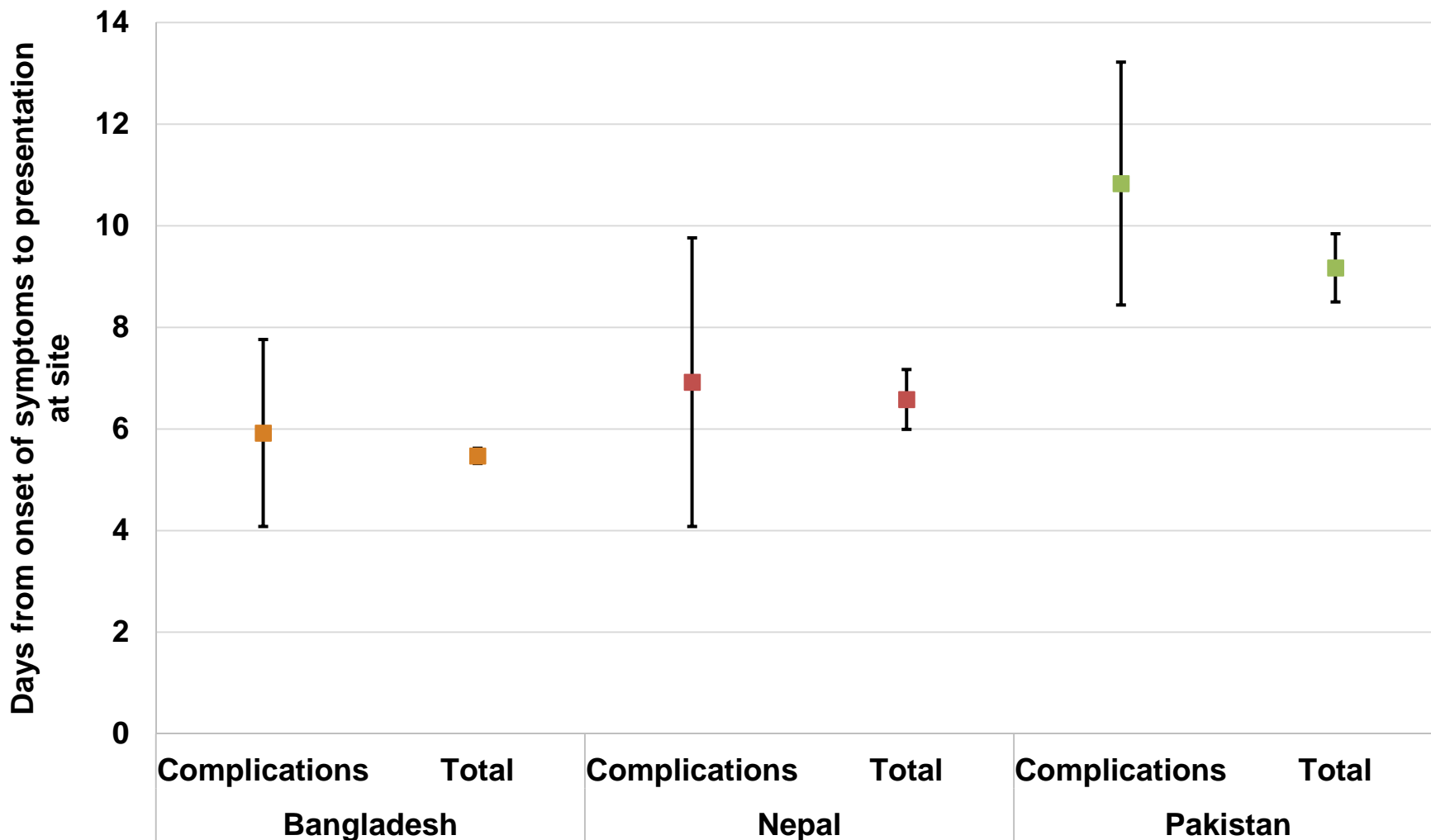
- Antimicrobial non-susceptibility Among Salmonella Typhi and Paratyphi A Isolates – Preliminary Results from SEAP project (presented by Muhammad Tahir Yousafzai)
- Mortality attributed to ileal perforations: Prospective data from a multi-centers enteric fever surveillance project in Pakistan (presented by Saqib Qazi)
- Validity of reported antibiotic use among suspected enteric fever cases in Nepal, Bangladesh and Pakistan (presented by Krista Vaidya)
- Healthcare-seeking patterns for individuals with suspected enteric fever (presented by Alex Yu)
- Incidence of Enteric Fever in Bangladesh, Nepal and Pakistan and Vaccination Implications: Results of the Surveillance for Enteric Fever in Asia Project (presented by Denise Garrett)
- Geo-Spatial reporting of Ceftriaxone resistant Salmonella typhi outbreak investigation in Hyderabad and spread to Karachi (presented by Abdul Momin Kazi)

Posters

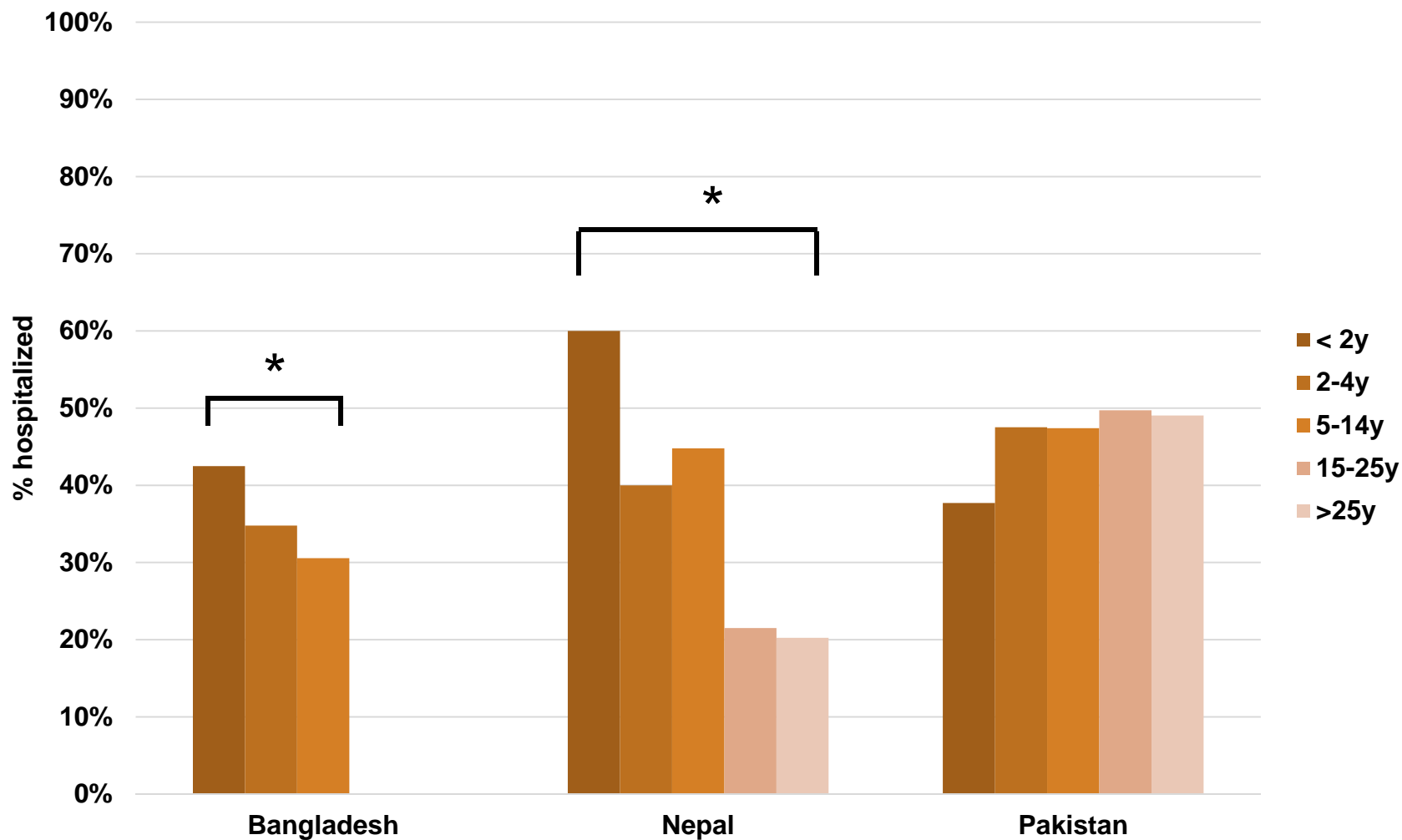
- Clinical predictors for culture-positive enteric fever in patients presenting with febrile illnesses in South Asian settings (presented by Kristen Aiemjoy)
- Comparison of cost of illness of extensively drug-resistant (XDR) vs. non-XDR typhoid fever in Pakistan: policy implications for typhoid vaccine (presented by Muhammad Tahir Yousafzai)
- Hospitalization of pediatric enteric fever cases during 2016-2018: Surveillance for Enteric Fever in Asia Project (SEAP), Bangladesh (presented by Shampa Saha)
- Intestinal perforations from enteric fever among children and adults: Data from prospective surveillance in Karachi, Pakistan (presented by Nasir Saddal)
- Use of geo spatial technique to identify catchment area of patient with typhoid fever – a hybrid utilization technique (presented by Momin Abdul Kazi)

Extra slides

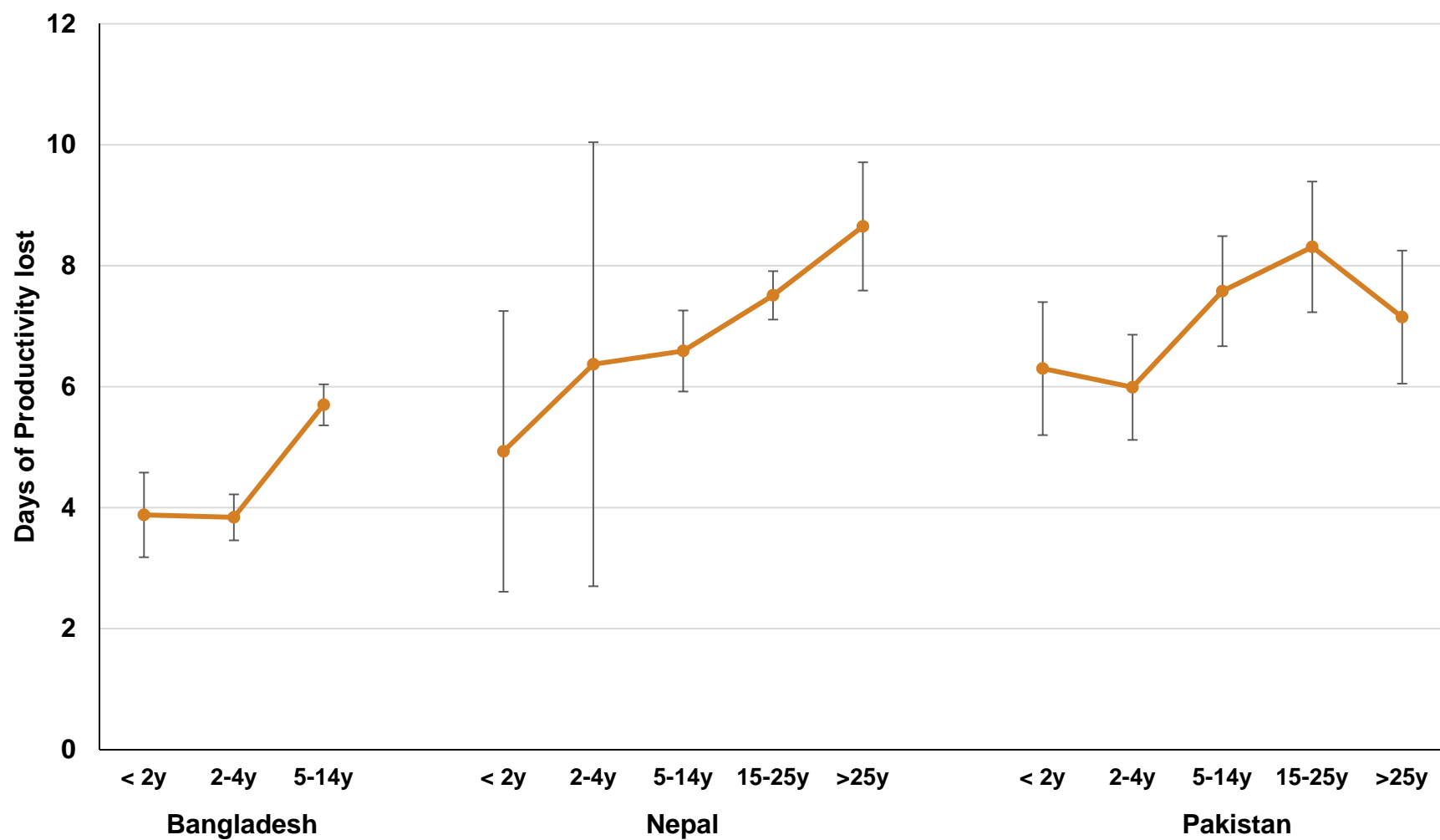
Time to seek care



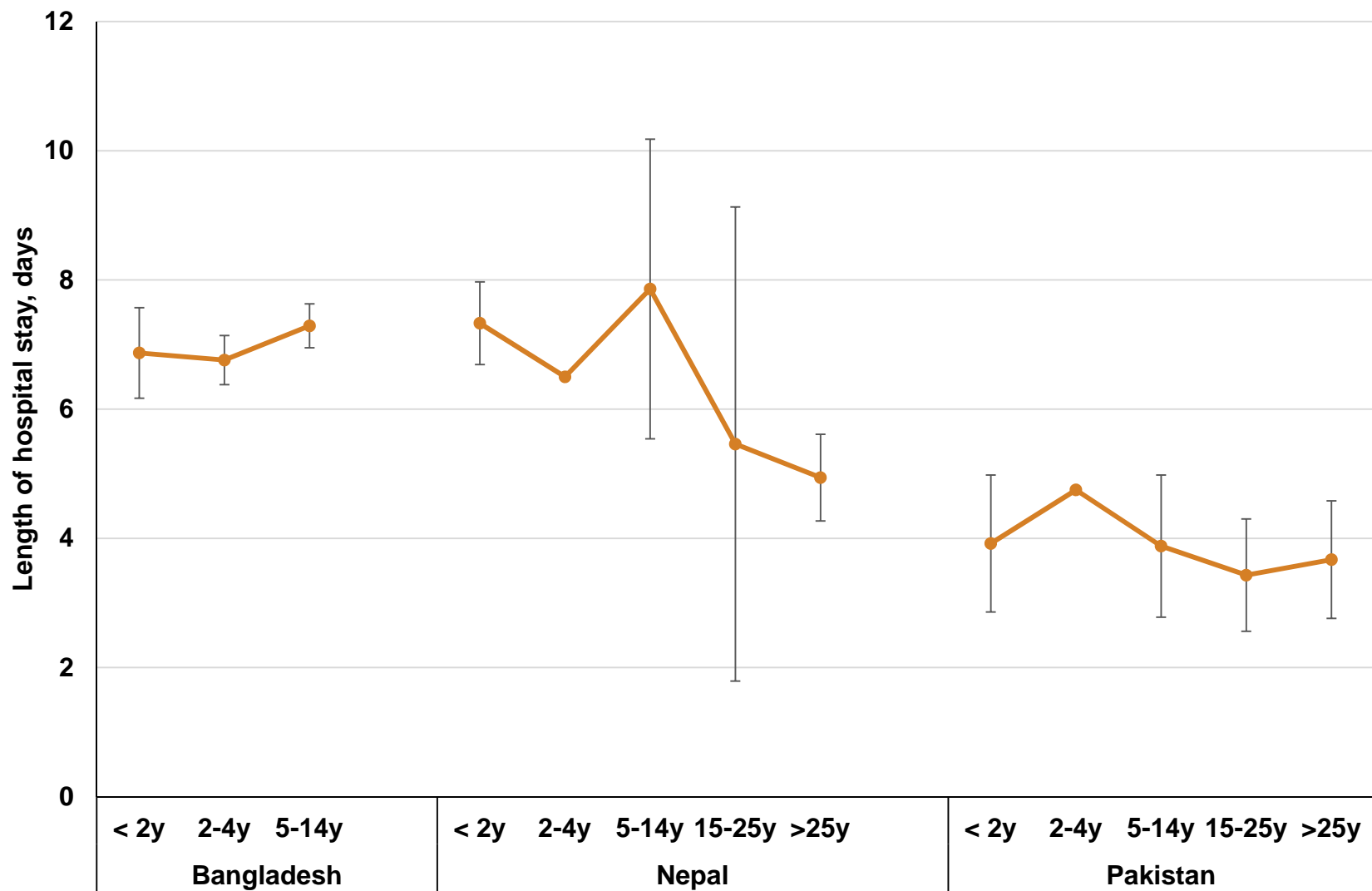
Hospitalization among hospital cases, by country and age group (n=3,720)



Days unable to do activities



Hospital length of stay



Differences in Antibiotic Use by Country

